In the Specification

Please insert the following paragraphs at page 6, beginning at line 24 of the specification:

In another embodiment, the invention includes an anesthetic agent delivery system for delivering balanced anesthesia to a patient through a breathing circuit and an IV which includes: (1) an anesthetic gas supply having a controller for controlling the amount of volatile anesthetic agent provided by the supply to the breathing circuit; (2) an intravenous anesthetic agent supply having a controller for controlling the amount of IV anesthetic agent administered to the patient intravenously; (3) an inspired gas analyzer for analyzing the concentration of anesthetic gas in the breathing circuit; (4) an expired gas analyzer for analyzing the patient's breath for concentration of at least one substance indicative of anesthetic agent concentrations in the patient's bloodstream that provides at least one signal to indicate the anesthetic agent concentration delivered to the patient; and (5) a system controller connected to each of the anesthetic supplies which receives the signal and controls the amount of anesthetic agents administered based on the signal.

In still a further embodiment, the invention includes an apparatus for administering balanced anesthesia to a patient including: (1) at least one supply of at least one intravenous anesthetic agent; (2) intravenous delivery means for controllably delivering the intravenous anesthetic agent to the patent; (3) at least one supply of at least one inhalational anesthetic agent; (4) a breathing circuit for delivery of said inhalational anesthetic agent; (5) an inspired gas analyzer for analyzing gas in the breathing circuit for the inhalational agent; (6) an expired gas analyzer for analyzing the patient's breath for concentration of at least one substance indicative of anesthetic agents in the patient's bloodstream that provides a signal to indicate anesthetic agent concentration delivered to the patient; (7) a system controller connected to the intravenous delivery means which receives the signal and controls the amount of anesthetic agent based on the signal; and (8) a system controller connected to the breathing circuit which receives the signal and controls the amount of anesthetic agent based on the signal.

Another embodiment includes a device for detecting target substances in a breathing circuit including: (1) at least one surface-acoustic wave sensor capable of detecting the presence of the target substance in inspired and/or expired gas, wherein the sensor responds to the target substance by a shift in the resonant frequency; (2)an oscillator circuit having the sensor as an active feedback element; (3) a frequency counter in communication with the oscillator circuit to measure oscillation frequency which corresponds to resonant frequency of the sensor; and (4) a processor for comparing the oscillation frequency with a previously measured oscillation frequency of the target substance and determining presence and concentration of the target substance therefrom.

Another embodiment includes a device for detecting target substances in a breathing circuit including: (1) a sensor having an array of polymers capable of detecting the presence of the target substance in inspired and/or expired gas, wherein the sensor responds to the target substance by changing the resistance in each polymer resulting in a pattern change in the sensor array; (2) a processor for receiving the change in resistance, comparing the change in resistance with a previously measured change in resistance, and identifying the presence of the target substance from the pattern change and the concentration of the substance from the amplitude.

Please insert the following paragraphs at page 15, beginning at line 10 of the specification:

Intravenous IV Anesthesia Delivery

During intravenous anesthesia, anesthetic agents are administered directly into a patient's bloodstream rather than administering gases through a breathing circuit. The administered drug may bind to proteins circulating in the blood, be absorbed into fat or exist in a "free" form. Drug bound to protein or absorbed in fat does not produce a pharmacological effect and exists in equilibrium with unbound drug. Numerous factors, including competition for binding sites on the protein from other drugs, the amount of fat in the body and the amount of protein produced, determine the equilibrium between bound and unbound drug. Unbound drug may participate directly in the pharmacological effect or be metabolized into a drug that produces the effect. Metabolism of the active drug often

leads to its removal from the bloodstream and termination of its effect. The drug effect can also be terminated by the excretion of the free drug. Free drug or a metabolite can be excreted in the urine or the digestive tract or in exhaled breath. The concentration in the blood (or plasma or serum) of such agents (e.g., propofol, alfentanil and remifentanil) is related to the clinical effect of the agent.

Generally, the exhalation gas stream comprises sequences or stages. At the beginning of exhalation there is an initial stage, the gas representative thereof coming from an anatomically inactive (deadspace) part of the respiratory system, in other words, from the mouth and upper respiratory tracts. This is followed by a plateau stage. Early in the plateau stage, the gas is a mixture of deadspace and metabolically active gases. The last portion of the exhaled breath comprises nothing but deep lung, so-called alveolar gas. This gas, which comes from the alveoli, is termed end-tidal gas. In one embodiment, the exhaled breath sample is collected at end-tidal breathing. Technology similar to that used for end-tidal carbon dioxide monitoring can be used to determine when the sample is collected. Airway pressure measurements afford another means of collecting samples at the appropriate phase of the respiratory cycle. Single or multiple samples collected by the side stream method are preferable, but if sensor acquisition time is reduced, in-line sampling may be used. In the former, samples are collected through an adapter at the proximal end of the endotracheal tube and drawn through thin bore tubing to the sensor chamber. Depending on the sample size and detector response time, gas may be collected on successive cycles. With in-line sampling, the sensor is placed proximal to the ET tube directly in the gas stream. Alternatively to sampling end-tidal gas, samples can be taken throughout the exhalation phase of respiration and average value determined and correlated with blood concentration.

The concentration of an anesthetic agent in the body is regulated both by the amount of the agent administered over a given time period and the rate at which the agent is eliminated from the body (metabolism). The present invention provides the steps of administering an agent to the subject and analyzing exhaled breath of the subject for concentration of unbound substances, active metabolites, or inactive metabolites after a suitable time period; the concentration indicates a characteristic of metabolism of the agent in the subject. The method may further include using a flow sensor to detect starting and completion of exhalation. The method further includes providing results

from the analysis and controlling the infusion pump for delivering the intravenous anesthesia agent based on the results. Moreover, a CPU may be provided as a data processing/control unit for automatically detecting the signal from the flow sensor to control sampling of exhaled breath. The CPU may further provide the analysis and control of the infusion pump or other administering means.

Methods for administering the agent are readily understood by those skilled in the art. For example, an infusion pump may be used. Compounds may be also administered parenterally, sublingually, transdermally, by i.v. bolus, and by continuous infusion. A number of suitable agents are available for administration as also known by those skilled in the art (Remifentanil -- Glaxo Wellcome, Propofol – Zeneca). Agents may also be those of amnesia, analgesia, muscle relaxation, and sedation agents or a combination thereof. Agents may be administered in an amount for analgesia, conscious sedation, or unconsciousness as known in the art. Patient characteristics may also be monitored during administration of the agent.

Concentration in the blood as measured by the breath analysis of the present invention for free agents or metabolites may indicate when the patient is receiving an anesthetic concentration (a high dose), an analgesic concentration (a low dose), or emerging from anesthesia as a result of a level that allows for full recovery. Even if there is wide variation in the metabolism or response to an anesthetic agent, knowledge of the exhaled breath concentration allows the anesthesiologist to know if the drug is accumulating in the blood, possibly leading to a dangerously deep level of anesthesia and/or a prolonged recovery time: or, the concentration is falling, possibly leading to inadequate anesthesia and premature emergence. Monitoring changes in concentration are, therefore, useful.

In another embodiment, the exhalation air is measured for free agent and/or metabolite concentration either continuously or periodically. From the exhalation air is extracted at least one measured free agent or metabolite concentration value. Numerous types of apparatus may be used to carry out the method of the present invention. In one embodiment, the apparatus includes a conventional flow channel through which exhalation air flows. The flow channel is provided with sensor elements for measuring free agent or metabolite concentration. Furthermore, the apparatus includes necessary output elements for delivering at least a measured concentration result to the

operator, if necessary. An alarm mechanism may also be provided. An instrument of similar type is shown in Figures 1 and 2 of U.S. Patent No. 5,971,937 incorporated herein by reference.

In one embodiment, once the level of concentration is measured, it is given numerical value (for example, 50 on a scale of 1 to 100). Should the concentration fall below that value, the new value would be indicative of a decrease in concentration. Should the concentration increase beyond that value, the new value would be indicative of an increase in concentration. This numerical scale would allow for easier monitoring of changes in concentration. The numerical scale would also allow for easier translation into control signals for alarms, outputs, charting, and control of external devices (e.g., infusion pump). The upper and lower limits could be set to indicate thresholds such as from no anesthetic effect to dangerous anesthetic levels.

Another preferred electronic nose technology of the present invention comprises an array of polymers, for example, 32 different polymers, each exposed to a substance. Each of the 32 individual polymers swells differently to the odor creating a change in the resistance of that membrane and generating an analog voltage in response to that specific substance ("signature"). The normalized change in resistance can then be transmitted to a processor to identify the type, quantity, and quality of the substance based on the pattern change in the sensor array. The unique response results in a distinct electrical fingerprint that is used to characterize the substance. The pattern of resistance changes of the array is diagnostic of the sample, while the amplitude of the pattern indicates the concentration of the sample.

The responses of the electronic nose to specific substances can be fully characterized using a combination of conventional gas sensor characterization techniques. For example, the sensor can be attached to a computer. The results can be displayed on the computer screen, stored, transmitted, etc. A data analyzer can compare a pattern of response to previously measured and characterized responses from known substances. The matching of those patterns can be performed using a number of techniques, including neural networks. By comparing the analog output from each of the 32 polymers to a "blank" or control, for example, a neural network can establish a pattern that is unique to that substance and subsequently learns to recognize that substance. The particular resistor geometries are selected to optimize the desired response to the particular substance being sensed. The

sensor of the present invention is preferably a self-calibrating polymer system suitable for liquid or gas phase biological solutions for a variety of substances simultaneously.

The sensor of the present invention might include integrated circuits (chips) manufactured in a modified vacuum chamber for Pulsed Laser Deposition of polymer coatings. It will operate the simultaneous thin-film deposition wave detection and obtain optimum conditions for high sensitivity of SAW sensors. The morphology and microstructure of biosensor coatings will be characterized as a function of process parameters.

The sensor used in the present invention may be modified so that patients can exhale directly into the device. For example, a mouthpiece or nosepiece will be provided for interfacing a patient with the device to readily transmit the exhaled breath to the sensor (See, e.g., U.S. Patent No. 5,042,501). The output from the neural network of the modified sensor should be similar when the same patient exhales directly into the device and when the exhaled gases are allowed to dry before they are sampled by the sensor.

The humidity in the exhaled gases represents a problem for certain electronic nose devices (albeit not SAW sensors) that only work with "dry" gases. When using such humidity sensitive devices, the present invention may adapt such electronic nose technology so that a patient can exhale directly into the device with a means to dehumidify the samples. This is accomplished by including a commercial dehumidifier or a heat moisture exchanger (HME), a device designed to prevent desiccation of the airway during ventilation with dry gases. Alternatively, the patient may exhale through their nose which is an anatomical, physiological dehumidifier to prevent dehydration during normal respiration. Alternatively, the sensor device can be fitted with a preconcentrator, which has some of the properties of a GC column. The gas sample is routed through the preconcentrator before being passed over the sensor array. By heating and volatilizing the gases, humidity is removed and the compound being measured (analyte) can be separated from potential interferents.

Preferably, in operation, the sensor will be used to identify a baseline spectrum for the patient prior to delivery, if necessary. This will prove beneficial for the detection of more than one drug if the patient receives more than one drug at a time and possible interference from different foods and odors in the stomach, mouth, esophagus and lungs.

Inhalational Anesthesia

Inhalation agents are generally administered through a breathing system. A breathing system is an assembly of components which connects the patient's airway to the anesthetic machine, from and into which the patient breathes. As known in the art, such systems generally include a fresh gas entry port/delivery tube through which the gases are delivered from the machine; a port to connect it to the patient's airway (oral airway, mask, endotracheal tube); a reservoir for gas; a expiratory port/valve through which the expired gas is vented to the atmosphere; a carbon dioxide absorber (for rebreathing); and tubes for connecting these components. Flow directing valves may or may not be used.

In an embodiment, side-stream monitoring is used. Moreover, a water trap, desiccant and/or filter may be used to remove water vapor and condensation from the sample. The device of the present invention continuously samples and measures inspired and exhaled (end-tidal) concentrations of respiratory gases. The monitored gases are both the physiologic gases found in the exhaled breath of patients (oxygen, carbon dioxide, and nitrogen), as well as those administered to the patient by the anesthesiologist in order to induce and maintain analgesia and anesthesia.

The sensors of the present invention may also monitor purity of gases at the entry port (fresh gas entry) and/or carrier gases. If multiple volatile anesthetic agents are connected to the circuit, an appropriate number of sensors may be included to detect each of such agents at the respective entry points as well as prior to inspiration.

Any number of sensors may be used at various points in the circuit to accomplish the desired monitoring. All of the sensors may connect to a single processor for analysis or use multiple processors. Similarly, the results of the monitoring may be displayed through a single display device or multiple display devices as desired. The method and apparatus of the present invention will detect and quantitate the concentration of the target substances.

Please insert the following paragraph at page 26, beginning at line 21 of the specification:

Moreover, sensing antibiotics with the exhaled breath detection method of the present invention, would allow for use of the method as a surrogate for blood antibiotic concentration. This would also be true for a wide range of medications for which blood concentration would be valuable. Exhaled breath detection using the method of the present invention may also evaluate pharmacodynamics and pharmacokinetics for both drug studies and in individual patients. Moreover, it may be used to sense endogenous compounds such as glucose, ketones and electrolytes which are normally found in blood.